only place where we advise that an airlock should be installed is at the entrance to the aseptic-processing facility that directly interfaces with the unclassified plan area.

We use this example as we believe it presented the clearest risk to assuring predictability of clean-room air quality. We liberalized some old standards including velocity. We state that velocity parameters established for each processing line should be justified and appropriate to maintain laminarity and air quality within the defined space.

We have relegated the old 90-feet-per-minute number to a footnote and acknowledged that it is often used. The design section of the concept paper stresses modern principles of reducing direct personnel involvement in aseptic operation through use of barriers and increased automation, moving personnel further and further away from the product.

As an example, the BFS Section notes that blow-field-seal operations are highly automated and require reduced human intervention. In order to increase latitude for new technologies, we have loosened up the language in other places, also.

This acknowledges that there may be a prevailing standard that should be, at the minimum, used for many of the applications, but there are also alternatives that are prominent.

One of the ways that we are assuring latitude is through liberal use of qualifying phrases such as "where appropriate," "where necessary," in some cases, "as necessary," "generally," "normally." As a means of comparing the '87 guidance to the concept paper, we did a search and found thirteen uses of such latitude phrases in the '87 guidance. We are now using fifty-three such qualifying phrases in the concept paper for latitude.

[Slide.]

We have been listening to comments from industry throughout our revision of the Aseptic Processing Guidance and it has impacted on the content of the concept paper you have before you today.

I hope I have provided a useful briefing this morning on some of the scientific and practical underpinnings behind our current thinking and risk-based philosophies that we believe are instrumental in preparing a revised guidance that

will be most useful to the industry and FDA.

At the end of the day, agreement on targeted cGMP systems to detect trends before product contamination occurs will achieve the goal that is shared by all of us, a higher confidence in sterile drug quality.

Thanks for your attention and we look forward to your comments.

DR. LEE: Thank you very much. Would you like to take one or two questions?

Any questions for Rick? If not, thank you.

Next on the agency is David Hussong. David spoke to this committee before and he is going to remind us about microbiology.

Microbiology Review Perspective

DR. HUSSONG: Good morning. Thank you for the opportunity to describe the review role in the regulation of sterile products.

[Slide.]

The regulatory oversight of drug manufacturing and marketing is done by multiple organizations at FDA each looking at different aspects of the product and process. Regulatory review of drug application is done by specialized

review scientists at the Centers. Review groups in the Center for Drug Evaluation are aligned according to scientific discipline.

Since sterile drug products are unique by their microbiological quality attribute of sterility, applications for sterile products are sent to the microbiologists for specialized review.

[Slide.]

During drug development in the investigational new drug, or IND, phase, products are reviewed to establish safety goals and minimize patient risk. Manufacturing process development is then monitored during the IND and data are generated on processing experiences.

By the time drug applications are submitted, manufacturing process experience has been gained. The product specification tests and acceptance criteria and process requirements are available, then, for regulatory review. The reviewer evaluates whether the manufacturer's process and controls are appropriate and whether the process controls answer the appropriate questions to assure process control.

The entire manufacturing process, its controls, the manufacturing facility need to be

appropriate for each specific product to be marketed.

[Slide.]

New drugs and generic drugs undergo product-quality microbiology review at the Center for Drugs. The microbiological reviewers evaluate the sterilization processes and their validation, test methods and acceptance criteria. According to the specific conditions of each product and process. [The text of part of this slide was not recorded.] Sterility is an absolute concept and it cannot be determined by any test.

Since there can be no absolute determination of sterility, then some risks must be accepted. Scientific evaluation can assess those risks related to each product and process.

[Slide.]

The guidance the reviewers used is provided in a 1994 document that was reprinted and is posted on the web. It defines what is to be submitted in application for drug products that will be marketed as sterile. The introduction to the 1994 Guidance states, "The efficacy of a given sterilization process for a specific drug product is evaluated on the basis of a series of protocols

and scientific experiences designed to demonstrate that the sterilization process and associated control procedures can reproducibly deliver a sterile product."

Data derived from experiments and controlled procedures allow certain conclusions to be drawn about the probability of nonsterile product units sterility assurance level. Based on the scientific validity of the protocol and the methods as well as the scientific validity of the results and conclusions, the Agency concludes that efficacy of the sterilization process is validated.

The 1994 Guidance details the elements of validation experiments, allows latitude for new experimental methods and criteria and provides for approval of these following critical review by experienced and qualified scientists. That document does not, however, provide specific cutoff points, limits and levels. Those are usually determined by the firm based on their experience and the product they are making.

[Slide.]

In the Center for Drugs, currently thirteen microbiologists perform these reviews. Eleven hold doctorate degrees with dissertations in

microbiology. Among the microbiologists doing the new drug reviews, there is over 120 years experience in FDA and/or sterile product manufacturing.

These reviewers include experts in heat processes, filtration, test methods development, microbial kinetics, environmental microbiology and clinical microbiology. Each has experience in aseptic-processing method and the staff had experience in guidance development.

The microbiologists in the Office of Pharmaceutical Science have offered commentary to this document and look forward to developing a rationale and cohesive document that will allow FDA to speak with one voice and with meaning.

It is not certain what forum this concept paper will take, whether it would be better to have it address FDA's training or the regulated industry. In a recent publication, the most recent from the Journal of Pharmaceutical Science, two prominent authors describe problems which have occurred recently where investigators have demanded tests or, in the words of these authors, unnecessary and they also describe them as dangerous.

We all know that there is additional work to be done on this concept paper and, certainly, they highlight an area which needs to be addressed. They conclude their commentary by saying that we need to get industry and FDA into a meaningful dialogue. I agree.

Regardless of the ultimate form of this document, the OPS microbiologists remain willing and able to provide assistance to the development of the document.

Thank you.

DR. LEE: Thank you, David.

Questions for David? If not, we have two more. Russ Madsen from the Parenteral Drug Association.

Industry Perspective

MR. MADSEN: Thank you. I wish to thank the FDA, all of the various divisions of FDA and groups within FDA and the advisory committee for inviting me to speak here this morning about FDA's new preliminary concept paper on sterile drug products produced by aseptic processing.

[Slide.]

You should have not overheads or slides, but you should have now in your packets the paper

that was put together by the PDA Special Task Force. We, at PDA, know that it is very difficult to get documents as complicated as an aseptic-processing guidance to an approvable state. After all, we are in the business of writing technical monographs and reports and getting them approved by a diverse bunch of smart people with varying opinions.

Those of us in industry in academia also serve on policy-setting committees and fight these battles every day. Therefore, we greatly appreciate the persistence and the effort the Agency has shown in producing this preliminary concept paper.

Every time we publish a new PDA technical report, there are two criticisms. It is too specific and, guess what, it is not specific enough. We also appreciate the creativity the Agency has demonstrated in publishing this as a concept paper to further the dialogue among all interested parties.

We are seeking this dialogue and we believe that it is essential to get the best possible work product. We applaud the fact that FDA has chosen to make the paper public at this

time and we are excited about the next steps.

[Slide.]

PDA believes the concept paper provides guidance useful to pharmaceutical companies and FDA field investigators. The guidance should enable inspected firms to know what to expect during FDA inspections of their aseptic processing areas and eliminate observations based on hearsay, outdated guidance or expectations resulting from what other firms did to comply with arguably overzealous FDA 483 observations.

There is a desire on the part of most individuals and companies to understand the aseptic-processing requirements and to comply. It is important that the final version is very clear on what types of limits and requirements are absolute requirements and what are suggestions where firms have the ability to make good scientific judgments based on the specifics of an operation.

We appreciate that the document does have areas where the need for such judgment is respected. The concept paper supports the advantages of isolators relative to conventional manned aseptic processing. We believe this will

encourage the use of isolation technology by firms that, having lacked guidance, delayed its implementation. It also provides the needed framework for open dialogue with FDA.

Finally, the availability of new guidance should eliminate use by the field of draft guidance which is unavailable to the inspected firms.

[Slide.]

PDA's concerns are grouped into categories; best practices and cGMP, technical issues and unconventional terminology, scope and harmonization.

[Slide.]

Departures from current industry practices include media fills conducted in worst-case environmental conditions, environmental sampling of critical surfaces that are terminally sterilized, the fact that isolators do not normally employ unidirectional air flows or redundant HEPA filters and there was no evidence to support that isolators must be housed in classified areas.

Further, the document goes on to say media fill should be conducted under environmental conditions that simulate normal as well as worst-case conditions of production. We believe

media fills which already tend to be worst-case because of growth-promotion properties of the medium and the extra manipulation sometimes required should be conducted under environmental conditions representative of normal production.

The document says that the monitoring program should cover all production shifts and include air, floors, walls and equipment surfaces including the critical surfaces in contact with the product and container closures. PDA believes that critical surface monitoring is not advisable because these surfaces are sterilized using validated processes. Monitoring these surfaces provides little meaningful information.

If the results are positive, it could mean that the surface contained one or more microorganisms or that it was contaminated by the act of sampling, itself. Even if negative, the result may not be meaningful because of less than perfect recovery efficiency.

Unidirectional air flow is generally unnecessary in closed isolators and the use of redundant HEPA or ULPA filters is not common practice and is unnecessary.

Finally, with respect to the need to

locate an isolator in a Class 10,000 or Class 100,000 environment, PDA believes isolators should be located in controlled but unclassified areas.

[Slide.]

Successful aseptic processing relies on strict adherence to specific well-defined procedures and on accurate knowledge of the critical factors that could result in nonsterile product if not properly controlled. Correct and consistent use of terminology with the industry and by FDA is critical to success.

The section on air filtration indicates that hot-air sterilizer vents should be equipped with membrane filters. HEPA filters should be used for this purpose, PDA believes. The document says that particle counts in Class 100 areas should be taken normally, not more than one foot away from the work site. But the concept paper fails to define what the work site is leading to unnecessary ambiguity and inconsistent interpretation.

The document says that air locks should be installed between the aseptic-processing area entrance and the adjoining uncontrolled area. Other interfaces such as personnel entries or the juncture of aseptic-processing room and its

adjacent room are also appropriate locations for air locks.

Typically, PDA believes that modern aseptic-processing areas are not equipped with air locks between the aseptic filling room and other portions of the APA. Finally, the terms alert limit and action limit should be changed to alert level and action level. Limits, we believe, are applicable to specifications while levels apply to process monitoring.

Specification--that is, limits--relates to a direct measurement of product quality that is required to be met by an official monograph or filed application. Exceeding an alert or action level does not produce an out-of-specification result.

[Slide.]

While the concept paper provides guidance in many areas, two of the most important questions are not addressed; that is, regarding media fills, how many units should be filled and how many positives are allowable. Other questions which remain largely unanswered are can a media fill be an exact model of an aseptic-manufacturing process with predictive quality which can be challenged by

going to extremes or is a media fill merely a demonstration that a manufacturer can aseptically fill a predetermined number of units under a given predetermined set of conditions without introducing detectable contamination.

There is little guidance offered relative to performance of the remainder of the aseptic-processing area outside the critical zone. Many aseptic-processing operations have extensive areas that are either Class B 100 nonunidirectional or Class C, Class 10,000. This is where personnel are located. The document should include more detailed guidance in these areas, we believe.

CIP/SIP technology; that is clean-in-place, sterilize-in-place technology. Although widely used today in aseptic processing, it is not addressed in the document.

Finally, the concept paper fails to provide a systematic rational approach to aseptic process control and risk elimination. While buildings, personnel and components are discussed, there is no clear discussion about how the process should be set up and how the segregation of product and the environment should be accomplished at each step in the process.

[Slide.]

Commenting on the 1987 Guidance Document, PDA said, "The PDA believes that the guidelines should include those areas of aseptic processing which are most likely to affect product stability, quality; namely the aseptic manipulations made by specially trained personnel during product handling and assembly. The physical means to sterilization employed by the industry have been validated to deliver sterility assurance level much greater than those which can be achieved by conventional aseptic processing.

The body of technical literature available on the validation of sterilization processes is adequate and considerable and could simply be referenced by the guideline. We believe these comments apply today to the current concept paper. While the concept paper builds on the framework of the 1987 guideline, we believe it should be focused on aseptic processing; that is, the control and manipulation of sterile components, closures and containers and the control, monitoring and maintenance of the aseptic-processing environment.

Subjects such as endotoxin control, equipment qualification and sterility testing are

covered in the literature in great detail. If FDA believes better information about these subjects is needed, we believe separate guidance documents would be appropriate.

[Slide.]

Finally, it would be most helpful to know when the document is providing guidance, should, and when it is defining requirements, shall, as these terms are used most frequently in isodocuments. Table 1 and all references to room classifications refer to Federal Standard 209(e). EIST, assigned by the GSA as the preparing activity organization for Federal Standard 209(e) has recommended that International Standard ISO 14644-1 superseded Federal standard 209(e) which became obsolete November 29, 2001.

The document goes on to say, "Air in the immediate proximity is of acceptable particulate quality when it has a per-cubic-foot particle count of no more than 100 in size range of 0.5 micron enlarger, Class 100, when counted at representative locations normally not more than one foot away from the work site within the air flow and during filling and closing operations."

We believe this section needs to be

harmonized with EU requirements where sample size and limits are quite different. The document says that each individual sample result should be evaluated for its significance by comparing to the alert or action limits. Averaging results can mask unacceptable localized conditions. A result at the action limit urges attention to the approaching action conditions.

The EU approach, on the other hand, is that environmental monitoring results should be averaged.

[Slide.]

Our recommendation are that the concept paper be reviewed by some kind of a committee, either an ad hoc committee of FDA Headquarters or industry or, perhaps PQRI, to resolve issues. The committee then submits the revised document to the FDA for review and approval. Final draft is issued for public comment and the revised aseptic-processing guidance is finally issued.

PDA believes the document provides a good platform for a final draft guidance meeting the needs of FDA Headquarters, ORA and the regulated industry. In order to quickly develop a final guidance document, we recommend that the concept

paper be reviewed by an ad hoc committee consisting of FDA Headquarters and field personnel as well as industry aseptic-processing experts.

We believe that media fills are an important component in assuring aseptic-processing operations are under control. But, even when a media fill consists of filling more than 100,000 units over three consecutive shifts, a media fill cannot assure the sterility of the next or any other production lot. We need to break the mold and find a reasonable alternative to massive media fills.

One possible solution would be to replace process-simulation tests or media fills with aseptic-process assessments or process-simulation evaluations in which the media fill would consist of a specified number of units--for example, 10,000--with a normal and atypical interventions running under normal line conditions with a specified acceptance criteria--for example, not more than one positive.

The media fill would be but one part of the aseptic-process assessment which would also include evaluation and documentation of environmental controls, environmental monitoring

results, gowning procedures, employee training, room-pressure differentials, air-flow patterns and maintenance.

The overall evaluation would provide a high degree of assurance that normal aseptic-processing operations result in products with high levels of sterility assurance.

We look forward to working with FDA, industry and other professional associations to develop a world-class aseptic-processing guidance document.

Thank you.

DR. LEE: Thank you very much. Any immediate comments? Yes?

DR. MOYE: I wonder if you could help me differentiate your concern about action limits and action levels. Could you say that again, please?

MR. MADSEN: An action level, we believe, is typically used for something that is related to a process. It is not a firm specification, and exceeding a level merely indicates the fact that the process has drifted from its normal state or, for example, some action needs to be taken. A limit, on the other hand, we consider a firm specification. So exceeding a limit would cause a

failure of a product, for example.

Typically, a limit is something like the USP specification or some number filed in an NDA or other form of application.

DR. MOYE: So, then, is your concern that the paper is inappropriately focussed on limits when it should be focussed on levels?

MR. MADSEN: In some cases and, in other cases, we believe that the paper is not specific enough. It doesn't provide enough guidance to know where a firm needs to be in terms of its compliance stance.

DR. MOYE: The action that is taken when a limit is exceeded should be different than the action that is taken when a level is exceeded?

MR. MADSEN: Typically, when a limit is exceeded, it results in a failure of the product or rejection of the product.

DR. MOYE: Thank you.

DR. LEE: Thank you very much. Bear in mind that we need some volunteers to review this paper.

The final presentation for this morning is from Professor Berit Reinmuller at the Royal Institute of Technology in Stockholm, Sweden. She

will be talking about design, control and contamination.

Design, Control and Contamination

DR. REINMULLER: Good morning.

[Slide.]

This presentation, airborne contamination in clean rooms, design matters, is based on research by Professor Ljungqvist and myself at Royal Institute of Technology.

[Slide.]

Our research has shown that the contamination risk can be described by the impact vector. The impact vector is depending on the velocity and the concentration of contaminants. The numerical value of K is the number of particles passing a unit area for the first time. The area is placed perpendicular to the particle flow.

[Slide.]

In a unidirectional flow, the particle impact can be calculated. If we have a continuous point source of contamination in the unidirectional flow, the concentration and particle impact can be calculated with this equation. After proper simplification, we can see that it is proportional to velocity and concentration.

[Slide.]

Class 100 environments become contaminated and the contamination ends up in the product. Here is a cross section of a unidirectional-flow unit with side walls connected directly to the filter. How can contaminations in the room air be intrained into this zone.

We have openings here and a flat surface perpendicular to the flow. If the surface is wide enough, we will have a stagnation region and the shape of the stagnation regions will depend on the size of the side walls, or the size of the opening. It is possible for room air to be intrained into the stagnation regions where contaminations move in an unpredictable way.

This is of special importance if small vials are processed close to the working surface.

[Slide.]

Another case is shown in this cross section. It is a unidirectional flow unit where the side walls do not connect to the filter and the filter, the clean air, goes out here. If this opening is too small, then room air that is intrained into to clean zone can be dispersed all over the clean zone and can be stuck in the

stagnation region.

[Slide.]

If we don't have any side walls at all, we will have an ingress region here where clean air and room air are mixed. We still have the stagnation region along the table and this situation is very sensitive to movements, movements of people, transport of material, doors that open, could cause ingress of room air in the clean zone and increase the risk of contamination of the product.

[Slide.]

This air movement you cannot see but visualization is an aid to understand the air movements. Here we have a unidirectional vertical flow unit. But, close to the horizontal surface, you can see the flow is horizontal. It sweeps along the bottle and, downstream, the bottle will have a way where contaminants are accumulated.

[Slide.]

Sometimes, the equipment we use in the clean zone--here is a vertical unidirectional flow unit. We have a small stopper ball here. The air moves nicely here. But around and above the stopper ball, it is a stagnation region where

contaminants are kept and it is a long cleanup period. Visualization is an aid but it is not enough for evaluating the aseptic processes.

[Slide.]

The LR method, the method for limitation of risks or similar approaches are very useful when evaluating aseptic processes and single interventions. The method is based on visualization of air movements to identify stagnation regions. A challenge test where a particle counter is placed in the critical area and simultaneously particles are generated outside or along interventions.

A risk factor is calculated and the risk factor is the number of particles measured in the critical area divided by the number of particles in the challenge. When the risk factor is less than 0.01 percent, less than 10^{-4} during the challenge test, then there is no risk of airborne contamination during ordinary operation conditions.

[Slide.]

I'm sorry for the slides here, but this should be a unidirectional air flow. We have sterile bottles here and a cover should be placed on the bottles. This is to illustrate how to

evaluate single interventions. The particle counter is set up close to the bottle opening. Particles are generated along the operator's arm and we compare manual operations placing the stopper on the bottle or using a tool placing the cover on the bottle.

In manual handling, we have a number, about 1,000 particles counted close to the bottle, a risk factor of 10^{-3} and an identified risk situation. Using the tool, generating particles in the same way, measuring at the same place, we find fourteen particles here. So, by changing from manual to an operation working with a tool instead takes the risk situation away.

[Slide.]

A case study by comparing different feeding or accumulation tables, the filling lines are the same. Rotating a feeding table about this side, the particle sensor above the table, measured risk factor, 10^{-1}, very high and that it was a bad design was confirmed by media fills.

We had much, much more than 0.1 percent contamination. We had close to 10.

A straight feeding table, the filing line exactly the same, the same particle sensor location

above the table, the same generation of particles outside the accumulation table, and less than 10^{-4} particles. Few particles measured and the risk factor less than 10^{-4} and no risk, and the media fills were, in fact, zero on the same filling line.

[Slide.]

I hope you can recognize an ampule filling line. It is infed from the sterilizing tunnel. The vials go around, or ampules. They are filled and closed and go out of the filling room there. It is all covered with unidirectional flow.

We tested the efficiency of the barrier. This is the filling line again from the sterilizing tunnel, the accumulation table. And then the filling zone. There are different doors here, one here. We placed a particle-counter sensor in the filling zone and then, in different spots along the line, generated particles outside above the doors wherever there was a small opening and below the side walls.

We measured zero, zero, and suddenly, here, above this door, when particles were generated here, we found particle ingress of room air in this locations. When particles were generated here on the table where you push the

buttons, we could also trace an ingress of room air to this. So, zero everywhere but two locations, two potential ways of ingress of room air. This didn't show on the media fills.

[Slide.]

So, to use the LR method or a similar approach improves the microbiological risk assessment. It is not depending on collection and growth of viable particles. It identifies dispersion routes of airborne contamination and it gives easy and easy-to-understand results.

[Slide.]

The ISO Class 5 operational status can be maintained in different ways. You can have tailor-made side walls. You can have restricted access barriers. You can have everything closed up in isolators and sometimes you need vertical separators along filling lines to prevent air movements and transport of contaminants along filling lines.

[Slide.]

Risk situations within the unidirectional flow are when obstacles are placed, and often we do place obstacles in the unidirectional flow. If they are close to the border of the critical zone,

entrainment from room air can occur. Wakes and vortices are formed. Large horizontal tables, large surfaces, cause stagnation regions. If you are processing small vials, then this is a problem.

[Slide.]

If we look at what the ISO 14698 says about biocontamination control, it says that zones at risk should be monitored in a reproducible way and a formal system for risk assessment should be in place to control factors affecting microbiological quality of the product.

[Slide.]

So risk assessment of airborne contamination requires good knowledge about the clean-room performance. It requires knowledge about the process in detail and also knowledge about the airborne dispersion of particles. Particles with or without microorganisms are transported in exactly the same way.

[Slide.]

Some requirements on the filling equipment used in unidirectional-flow radials. The should be easy to clean and have an aerodynamic design, reliable mechanization in order to prevent unnecessary interventions, a certain ruggedness,

simple orientation and unscrambling. It should not be necessary to build a filling machine of 96 parts in the laminar flow, unidirectional flow.

If possible, it should have good ergonomics for the people working along the line.

[Slide.]

When risk assessment is performed in a proper way and the safety is measured and evaluated, then we can design safety into the process and the risk of contamination failures can be prevented.

[Slide.]

This is the most common contamination sourcing in clean rooms. But today's clean-room clothing, clean-room underwear, clean-room dresses, is much more efficient than it was twenty-five years ago.

[Slide.]

Aseptic production areas do not only consist of the filling room. There are the rooms around it. And we have flows between rooms, between openings. If we have constant pressure differences, then the pressure differences will cause a flow of air. For example, a sterilizing tunnel opening on a filling line and a pressure

difference of 15 Pascal means that you will have a velocity of 5 meters per second through the tunnel opening. That air must be provided by the unidirectional flow above. Otherwise, room air will be entrained into the sterilizing tunnel.

Small openings, an opening 20 centimeters in diameter, will give the same outflow, 5 meters per second if you have a 15 Pascal pressure difference, and a flow of about 4 cubic feet per second out of the room.

One comment about the door. When you open a door, you lose the overpressure.

[Slide.]

When there are temperature differences, there are air flows. At the autoclaves, we often have temperature differences when the autoclave opens. Lyophilizers and sometimes at doors, doors between, for example, the changing room and the filling room, there might be temperature differences. When the temperature differences are four degrees or more, then the 10 Pascal overpressure cannot prevent ingress of air from the dirtier area into the cleaner one.

[Slide.]

This illustrates the case with the hot

autoclave being opened. The hot air escapes here and room air is entrained here over the load. We have a 40 degree temperature difference, 40 degrees Kelvin. Then the opening of an autoclave, 1 by 1 meter, the flow in the autoclave and out of the autoclave is approximately 1 cubic meter per second.

[Slide.]

A decreasing temperature for the lyophilizer, if we have 25 degrees in the room, -2 degrees in the lyophilizer, it is a difference of 25 degrees, then air will come this way. The cold air, when the door is open, will flow out and be replaced by air this way. How much air do you need to compensate for this? It can be calculated and you can predict, calculate, how large a flow you need here to protect the lyophilizer and to transport contaminations away from men working in front of it. It can all be calculated.

[Slide.]

If the autoclave looks like this, a huge high opening and let's say that 25 degrees will take in almost 1 cubic meter per second here and 1 cubic meter per second out. Instead, if there is a pit opening 20 centimeters high and the same width,

1.6 meter, the flow will, instead, be 1 cubic foot per second. So the difference here in the opening size affects the volume of the flows.

[Slide.]

There is a need to assess the situations of airborne contamination in a scientific way and design certainly matters.

Thank you.

DR. LEE: Thank you very much. Are there any questions? If not, there is some food for thought. You have the concept paper in front of you. You have the background behind this concept paper. You heard the presentations that help you to analyze this paper and engage in some lively discussions after lunch.

So, if there are no other questions, I propose that we adjourn until 1 o'clock when we have the open public hearing. I think there are six individuals. You know exactly who you are, what your order is and how much time you have and I will be watching the time very closely.

Are there any remarks from the administrative side? If not, thank you very much and I will see you back at 1 o'clock.

[Whereupon, at 11:38 a.m., the proceedings

at

were recessed to be resumed at 1 o'clock p.m.]

A F T E R N O O N P R O C E E D I N G S

[1:00 p.m.]

DR. LEE: The next item is the open public hearing. I have six individuals. Please excuse me if I pronounce your name incorrectly. Let me go by the first name. Maybe that is easier. Ken? Ken, you have five minutes.

Open Public Hearing

DR. MUHVICH: I recognize the importance of this concept paper and it is important for the FDA and the industry to get together and get some consensus now rather than later. However, I would like to focus on something that I think everyone is missing. If it is not the elephant, they are ignoring it anyway.

Aseptic technique in this industry is, sad to say, not very good. If the industry does their job and the FDA does their job, then that will provide a lot in the way of sterility assurance for the products that are being put out on the street. Because of the nature of cGMP these days and the quality of systems inspection and so forth, much time is spent by FDA investigators in conference rooms looking at stacks of investigations to see if people are doing a good job with that and little

time is spent watching filling operations to discover that aseptic technique is not what it should be.

I learned aseptic technique as a young corpsman in the Navy on a hospital ship in Viet Nam. If the aseptic technique--if I had the kind of aseptic technique then that people have in clean rooms nowadays, the OR nurse would have smacked me in the head and sent me away until I could come back again.

People always talk about retraining in this but there is no guidance in the industry--I just want to make the point the supervisors in clean rooms are not doing a good job at all. They are there. They observe people with breaches in aseptic technique and they do nothing about it.

Aseptic processing and aseptic technique have to be 100 percent every day. There can't be a day taken off or then you are going to have the types of things that Rick Friedman was talking about earlier.

I recognize the value of this guidance document but I think people need to refocus--I didn't hear anybody mention the word aseptic technique today and it is typically not mentioned

anywhere. But the key to aseptic processing is proper aseptic technique. There aren't any people that I see, or very few people, I should say, that really know what it is and how to teach it and it is a big problem for this industry, as I see it.

Thank you very much.

DR. LEE: Thank you, Ken.

Any questions for Ken? David Miner who actually was my bodyguard from the hotel to here this morning.

MR. MINER: Little did I know how exciting it was going to be walking over here from the hotel this morning. I am Dave Miner. I am with Lily and I am speaking on behalf of PhRMA and I am going to echo things you have heard several times already.

We do believe firmly that good science-based GMP guidance could provide important advantages for all stakeholders in this process, better assurance of quality products for consumers, companies less likely to make mistakes and allow FDA to focus on the truly gray areas and the areas where things are changing or need to change instead of things that should be common accepted standard practice.

In that light, we welcome the concept

paper and the release of the concept paper. We know that significant effort has gone into carrying it this far. New guidance is desperately needed in this particular area and it is a positive step to publish a draft.

As you heard a bit from Russ and I am sure there will be many other comments going forward, this draft needs significant improvement. But, folks; that's normal. That is where is should be. That is part of the process of getting the good guidance is putting something out there and having a dialogue around it and talking about it.

So we should feel very good that we have it out there. Hopefully, many of things, as Rick talked about this morning, that are already included there are positive steps. Some others are going to need adjustment, but that is part of the process.

Which brings me to the importance of process. I believe, really, to get good GMP guidance you have got to have good process. If you don't have a good process, number one, it will never get out. Number two, it has no chance of being timely. This is an area that is moving too fast for us to wait five to ten years to get

something out. By the time you get something out in five or ten years, it will have changed on you.

So good process is really critical going forward. I think that process is most likely to be rapid, effective and provide cost-efficient gains in product quality over time if it comes to an active dialogue with industry, academia and regulators all talking.

We, in industry, have long been criticized and criticized ourselves when people in discovery research took a compound and "threw it over the wall to development," or development took a product and threw it over the wall to manufacturing. A very valid criticism.

The same applies when you think about guidance. You really need to have folks talking to each other in real time to think through what are the best ways to do things.

So, in that light, we wonder, can the progression of the concept paper and the draft guidance to follow perhaps serve as a pilot for a better process. Can PQRIs serve as a key incubator for this better guidance. PQRI brings those key parties together. We would like to see PQRI tackling key aspects of aseptic processing among

the technical experts that need to be brought together.

Specifically, on the concept paper, I am not going to comment, with just one exception, and that is that the importance of the regulatory system, not just guidance but all aspects of the system, encouraging positive change. Take, for example, the use of isolators. There is general agreement that a well-designed isolator can provide significant improvement over conventional aseptic processing.

This is, in fact, reflected in the opening part of the concept paper and there is new section, Appendix 1, on isolators. However, when you think about the system, to date, the regulatory environment in the U.S. appears to actually have discouraged the introduction of isolators, if you look at the update of isolators in the U.S. as compared to the update in Europe.

So, we need to very careful and thoughtful about how we regulate so that we encourage good change.

Let me just pick out one example. It is a very small one, but just as an illustration of how we need to be careful. Line 1458 in the Appendix I

calls for a six-log reduction of BIs on the inner surfaces of isolators during their decontamination.

By contrast--this is the case of isolators where we should be having better protection--there is no such requirement for the less protective conventional aseptic processing environment. So you have moved to a more protective environment and you have added a new expectation. Why is that potentially a problem?

The cycle times that are required for vapor-phase hydrogen peroxide to get to that level of decontamination, maybe you have to increase to realize that. You might be confident that all the surface areas that you happen to have inside that isolator are going to get there which may cause your management to question the viability of the project and whether you should be going forward with it at all.

This one requirement, being a new requirement, has the potential, along with other things, to discourage what I think we all would agree, when it is done right, is good change. So we just raise that as a cautionary note about thinking through how this will encourage good change, which we all need.

So, to conclude, PhRMA applauds the release of the concept paper and we look forward to looking with the Agency as it drives forward to final guidance.

Thanks.

DR. LEE: Thank you. Questions for David?

DR. KIBBE: I have a couple of questions, since you are the industry and standing there smiling at me. We saw some recalls on that bar graph which interested me, that there was such a big dramatic jump. I know you can't answer why all those were recalled but, just out of curiosity within your own shop, when you have a batch failure, is it more often a sterility problem or more often something else.

MR. MINER: I am not sure I can answer that question off the top of my head, but one thing to think about is how many aspects, and Rick talked about this this morning--how many aspects do you have to control when you are talking about an aseptically processed product.

So if you think strictly in terms of the number of systems that you have to control and the potential for something to go wrong, your odds are greater just because of the number of things that

you are trying to control. I can't quote statistics off the top of my head.

Now, I would say, with regard to that recalls thing, I think it would be helpful to look behind that as you try to get to root-cause analysis for any problem that you run into, and understand what are the factors that are driving that, what led to the circumstances where you had those recalls and pull those out, each and every one that is significant in there.

DR. KIBBE: But you don't have any sense of--what I am really getting at is how often do we say, okay, we are not going to release this batch because we know that there is a problem or that we think there might be and we can't prove it one way or the other.

MR. MINER: Oh, that definitely happens. Without the appropriate documentation, you can't go forward and release the product against the risk of somebody questioning whether--even if you thought it was all right, if you don't have the documentation, you can't release that product.

DR. KIBBE: Thanks.

DR. LEE: Thank you.

The next person is Professor Ljungqvist

from Sweden.

PROFESSOR LJUNGQVIST: Good morning.

[Slide.]

A microscopic vortex in a clean room is a fact. What do you know about vortices? Well, they will accumulate contaminants.

[Slide.]

That has been proved as well in theory as in practice experimentally. Here you can see the theoretical equation and, if you are smart enough, you see the concentration accumulation.

[Slide.]

But that is not so easy, so I show a smoke filter instead. Every photo is taken with intervals of a couple of seconds. You can see that accumulation effect of the vortex. What you should be aware of, vortices will accumulate contaminants.

[Slide.]

Laminar air flow is cold in the draft but it should be unidirectional according to my opinion. Here you have laminar air flow when you see particles follow the stream line all the way. Here you have turbulent air flow when you have the small fluctuations around. Most Class A environment in the pharmaceutical industry has a

parallel flow like this. So the right wording which I use should be unidirectional air flow and skip laminar flow.

[Slide.]

If you have obstacles in unidirectional air flow, and it is a low velocity, it will, in the beginning be a smooth stream line, smooth air patterns. But if you increase the velocities, you first will get wake vortices and, after that, vortex streets. If you increase the velocity more, you will be a high range of turbulencies.

[Slide.]

Here we have a practical case. You have a filter fixture here. First, you get the wake vortices and then the vortex street. In this case, you also get irritational vortices. By the way, you can see a filter down here in the critical region of such a vortex.

You are discussing, in the draft, about the sweeping action. That means that this should take away these contaminants in this region, also. You also write in the draft that one should measure at this level and then you said "or" at this level. I think it is very important that you measure also velocities in those levels.

So, in Line 257, an "or" should be changed to "and" because you should measure as well up here as down here.

[Slide.]

Here, if we have a person in a unidirectional air flow--in this case, it is a horizontal unidirectional air flow. You see the smoke source here and it goes out very smoothly. The air goes like this passing the person. Everything is okay.

[Slide.]

What would happen if the person raises his hands and arms? Then you get a sudden change of the pattern. In some cases, that can be very dangerous for the product or the man.

[Slide.]

Here is a horizontal unidirectional air flow unit. Here we have the HEPA-filtered air and the main direction of the air movements is like that. Here we have the smoke source and you can see how the smoke goes from this region and out in the ambient air which is the intention, of course.

But even if you have some bottles here and you have the smoke source here, it will go, not out. It will go back because of the way it

vortices up to the critical region and then out.

[Slide.]

Still, we have a main air flow out like this and the smoke source here. But you move your hand like this and then the contaminants will follow from the person into the critical region.

[Slide.]

In this case, you have the vertical air flow and the machinery. The moving machinery will also give disturbances, wake vortices, et cetera, and you see the complex and rather difficult situation in this region.

[Slide.]

I would only like to say the part in the draft be Lines 272 to 282 stresses the importance of knowledge about personnel movements which I think is important that we can read it there.

I have five minutes. After having heard Dr. Reinmuller's and my presentation, you can understand, see immediately, of course, that this picture does not show good aseptic conditions, if you are trained, of course.

Thank you very much.

DR. LEE: Any questions?

MR. MUNSON: If you take your velocity

measurements down basically at work height or whatever where the vortexes are, how do you get accurate readings?

PROFESSOR LJUNGQVIST: First of all, you shall not have that vortex system. If you have it, you don't get accurate. But you should have smoke visualization telling you it is not accurate.

MR. MUNSON: Okay.

PROFESSOR LJUNGQVIST: But if you get a sweeping action, you should be able to measure that and get an actual value because, with the sweeping action, you have the main flow direction and that main flow direction is capable to be measured. But, of course, you also see it with your smoke visualization. But I think you shall do both.

MR. MUNSON: Right. It has just been my experience that when you get down that--it gets very, very hard to get good readings because of the direction of the air.

PROFESSOR LJUNGQVIST: You should look at it. If you take that away, no one--I know that persons in the Nordic countries, they put an "or" there. That means that we don't need to bother. I will have the "and" because they should bother with that region.

DR. LEE: Thank you very much.

Mr. Becker from Merck.

MR. BECKER: Good afternoon, everyone. My name is Martyn Becker and I am here representing Merck and Company. I would like thank you all for giving me the opportunity to put forward the views of Merck on the document that has been published now by FDA, and thank you very much for that.

The document does provide good basic philosophical guidance for aseptic processing. What I would like to just put before you are some opportunities for clarification which exist within the document.

We think that there are concepts that would be beneficial to enlarge including qualification of the scope of processes that are referred to in the paper, specifically enlargement upon guidance that is given in the document. I offer some examples; references to limited aspects of bulk processing. The document indicates that it only applies itself in a very limited fashion to bulk processing

So the important points of some of the thought processes are not references; for example, aseptic processing of bulk materials post final

sterilization and the use of true closed systems.

There is a section on isolators, but it doesn't reference the use of different types and specifications within the industry. The relevance of the guidance to classes of pharmaceutical products that are not required to be sterile according to filing or usage but are processed aseptically because of the nature of the product. I am referring to things like oral vaccines here.

It would be beneficial to make sure that the terminology used is consistent throughout the document so that concepts contained in the paper can be most effectively realized--one of the biggest examples is a reference to ISO 14644 that you have already seen--which do not appear to harmonize with what is now obsolete in terms of Federal Standard 209(e) and the references throughout the paper are in the Federal Standard terminology.

The industry hoped that there would be some kind of steps towards harmonization of area classifications with regard to the European Annex 1 classifications and ISO 14644, especially since it has been stated within the revision of the Annex I, the European Annex I, process that it is intended

to harmonize with ISO 14644 for a particular specification.

We fully support the use of a science-based approach for the areas with in the concept paper although there are a number of these areas which are unclear. There is some sort of confusion, I think, with the table on Page 3 in terms of area classifications which appear to simultaneously refer to a less than 3 CFU limit for Class 100 which is immediately, then, modified by the statement that there should be normally no contamination.

It is not clear what the reference to 1 in 1000 units is within the process-simulation section. It is not clear what this is meant to convey. It is agreed that the use of inappropriate statistics is not meaningful for simulation acceptance, but it should be acknowledged that what is essentially a sampling process, within that process, there should be some sort of defined mechanism to apply the sample to the whole population of the simulation.

Also, you could cite things like filter-integrity testing with regard to the intent or the expected criteria, specific examples being

the guidance's relevance to hydrophobic vent filters, or the requirement to test depyrogenation tunnel filters in in-use conditions, which could be a safety issue as these might be up to 300 degrees Celsius.

Process-simulation requirements focus upon the simulation of the actual process and yet the extremes of the temperature and humidity are required which is not representative of the process as carried out. There is also no indication of what worst-case environmental conditions actually means.

A very important point is container-closure integrity which is important with regard to the aseptic-process validation, but there is very little reference to it. If it is required that another guidance document be referred to, then we would recommend that it specifically be referred to in the back of the document.

Isolator-background classification requirements are also unclear for all isolator types since it might be inappropriate to apply environmental criteria for open manufacturing isolators as well as closed testing ones.

In summary, we acknowledge that regulatory

documents are not normally over-prescriptive but rely upon the use of good science to make sure that sound justifications exist for the rationales used. We would support additional editorial input to assure a consistent implementation and the interpretation of requirements. Also, we support the assurance of the guidance process by supporting effective training of field investigators that will eventually be responsible for implementation of this guidance when it becomes a guidance document.

Lastly, it is our opinion that for such a document of such fundamental importance to the aseptic-processing industry worldwide, an appropriate review periods, say 90 days, would be at least appropriate for its review and full comment.

We support the manufacturing-subcommittee incentive. It is very beneficial in view of the global regulatory environment worldwide.

Thank you very much.

DR. LEE: Thank you.

Any questions for Marty? Very clear. Thank you. Maurice Phelan?

MR. PHELAN: Thank you. My name is Maurice Phelan and I am here on behalf of Millipore

Corporation primarily to thank the FDA, all of the FDA participants, in producing this document and the members of the committee for what has been a long way to document, I believe.

In particular, we would like to thank you for the inclusions. From talking to some of my colleagues and some of our industry partners, the rider inside of that document which really sort of tells us that, for things like introductions of new technologies, there is clearly, from our point of view, the latitude to implement new technologies assuming that there has been appropriate validation conducted around those and that, to us, is very important given some of the programs which we have in place to help this industry in the area of aseptic processing.

We understand, by the way, truly understand, that filters are a very, very small part of an aseptic process. But, to Ken's point earlier, filters work very well. But, if they are not connected properly, if good aseptic technique is not used, they probably won't do as well as one might think, not the fault of the filter.

[Slide.]

Just one area which I believe we are going

to further comment on, and by the way, as an organization, and personally, we would be delighted to participate in any review processes that result from the decisions of the committee or this meeting--rapid-transfer technology is referred to on Page 37, aseptic processing and isolators.

We intend to put forward some data as well as a discussion on the fact that there is a clear differentiation between decontamination, transfer and the ability to sterile-transfer through an appropriate port using sterilization sources such as UV technology 254 and UV. That assumes, of course, that the appropriate, well-thought-out and demonstrated validation package associated with that sterilization source can pass along with it.

We are currently working on some data in that regard to support some of the comments that we are going to make, but we believe that technologies like this primarily benefit this industry in the area of removing personnel ingress, particularly in the sterile-isolator area.

[Slide.]

Moving on, briefly, to the filtration portion and, in fact, the filtration-efficacy portion of the concept brief, Page 21, there is a

discussion of porosity of filters and pore-size ratings. This is really a semantic issue but the statement where 0.2 micron are smaller, if that were literally processed, it would, in fact, rule out something like a 0.22 micron rated filter.

That is not really the issue so much as I think there is an opportunity to have a discussion around decoupling pore-size rating and sterilizing-grade efficiency and, potentially, to open a further discussion where we talk about sterilizing-grade filtration as a function of the validation studies that have been performed around the process and the individual filtration step and not the nominal rating of a filter.

To that end, we would be inputting and further commenting on methods for validation of filtration efficacy building on some of the technical reports that are being produced by the PDA along with and to the point of the gentleman who spoke before me from Merck and validation of integrity-test methods for hydrophobic vent and gas filters and, of course, liquid-sterilizing grade filtration.

Lastly, although the concept brief does allow for the discussion of endotoxin removal by

membranes, there are some technologies, membrane-based technologies, in particular charged membrane technologies, which will remove very, very efficiently endotoxin from liquid streams and, although there is a lot of latitude in this document, as Rick Friedman pointed out this morning with the fifty-three broader statements where the word "appropriate" is used and generally is used, it may well be worthwhile having a discussion around that during the comment phase.

That is really all that I would like to say this afternoon. Thank you very much and, again, we would be delighted to be involved in any type of further processes that will help put our expertise together with your expertise to produce a great document.

Thank you.

DR. LEE: Thank you very much.

The final presentation is by Dimitri.

MR. WIRCHANSKY: Good afternoon. My name is Dimitri Wirchansky.

[Slide.]

I am a pharmaceutical technology specialist for Jacobs Engineering in Conshohocken, Pennsylvania. I also happen to be the Isolation

Technology Interest Group leader for PDA. In the beginning of the year, PDA put out a survey for the use of isolators and we wanted to find out how the industry was using isolators.

[Slide.]

The results of this survey were presented at an Isolation Technology Conference by PDA April into May of this year. Rick Friedman asked me if I would come to discuss a couple of the results of that survey as it relates to the sterilization or, rather, the decontamination of the isolator background. Also, I have addressed a few comments to Appendix I dealing with isolators.

The survey was sent out. We got fifteen respondents. This slide shows the different applications of those respondents.

[Slide.]

I picked out the ones that I thought were most appropriate, that being sterility testing and manufacturing. We had fourteen respondents for sterility testing. Most people were doing sterility testing. One response was for some specialized testing.

[Slide.]

Of those respondents, two reported a

decontamination to a 3-lot reduction. Ten reported a six-log reduction and one reported a sub-cycle, 10^{-6}, which really went to 10^{-12}. Then there were some other comments around 10^{-6}. So, if you look at it percentagewise, you have about 14 percent on three-log reduction, 71 percent for six-log reduction and 7 percent for that double-kill cycle.

[Slide.]

This looks at aseptic manufacturing and the applications include formulation, low-speed filling, higher-speed filling and some other more specialized applications.

[Slide.]

In this case, one respondent reported a five-log reduction. Six reported a six-log reduction. Then there was another comment around a total deactivation of BIs, 10^{-6}, which I counted as a six-log reduction. Then we had one other application using a three-log reduction for wrapped presterilized components or tubs and these are probably the presterilized syringes. That was a three-log reduction.

So we have 11 percent for a five-log reduction, 78 percent for a six-log reduction and 11 percent with a three-log reduction for that

specific application. As I say, the idea behind this was just to get an understanding of how people were using the decontamination process in the isolators.

[Slide.]

The introduction to Appendix I; I think coming out and saying the well-designed positive-pressure barrier isolator is better than conventional aseptic processing, I thing that is a very good thing to say because I go out and I help people design and build pharmaceutical plants. Some clients will come to me and they will say, "Okay; we are going to build a new aseptic operation. I want to use isolation technology in this application," and so on.

Other clients will say, "I don't want to use isolation technology in this application," because, basically, they are afraid that if they make that decision, by the time they get their assets producing that they will have spent a lot of extra money and wasted a lot of time and they have a concern in that area.

I think that a statement like this at least shows that the Agency is trying to be supportive of this technology and help advance the

technology. We also have clients that aren't quite too sure whether they want to go towards the isolator or to go to some form of a modified conventional technology.

I have been working in aseptic manufacturing since '71, so I am kind of getting to be an old guy, but I haven't really seen anything that has made an impact in aseptic processing the way isolation technology has. So I think, as a leader of the Isolation Technology Interest Group, it is my goal to try to foster the advancement of this technology in good applications throughout the industry.

[Slide.]

These comments kind of refer to some specific items about the isolators. I didn't try to be all-inclusive but just to get a flavor for what I see for some of these things. Glove integrity; this is Section A.2. There are some strong comments. "With every use, gloves should be visually evaluated for any macroscopic physical defect." You can read the rest of what is up there.

This is true. If you have a noticeable tear, that is a problem. Where you get to have an

issue is like what if it is not noticeable. Then you may find it later or how do you deal with this. People that use isolators are concerned about this.

I think that the statement in the proposed regulations focusses very much on the gloves. That is important because gloves are important. But I think it should be part of a comprehensive operating and maintenance plan for the isolators. I think this plan should include measure to minimize the risks posed by the glove such as under-gloving or over-gloving.

Proper aseptic technique requires the use of a sterilized implement such as forceps or some other thing for the intervention to critical sites. Basically, you shouldn't be sticking your gloved hand, even though it is an isolator glove, into the aseptic part of the process.

During discussions at the Isolation Technology Interest Group, the users were very concerned about gloves. Different companies have developed different strategies, putting on gloves over the--the operator would put a sterilized glove over the hand that went into the glove. One company talked about how they sanitized the inside of that glove.

Of course, they decontaminated the outside of the glove as part of the decontamination cycle for the isolator. One company also talked about putting a glove over that glove sort of like to protect the isolator glove. So, the people that are using these things care about that and it is a concern for them.

I think it is a valid concern. I just think that it has to be looked at as part of the whole because, if somebody is doing a procedure to try to minimize the risk of the glove, that we should look at that as part of the whole procedure and not just say, "Oh, well; there is a hole in the glove. What does that mean?" Has that glove been tested afterwards? Has it been plated? Do we find counts there, those types of issues.

[Slide.]

This one describes air flow. I think we have had two people already discuss air flow quite a bit. Where it says, "In most sound designs, air showers over the critical zone once and systematically exhausted," this pretty much describes a unidirectional-flow isolator. Those typically find application in aseptic filling.

Turbulent-flow isolators also have

application, perhaps more in formulation with or without containment because sometimes we make aseptic products that are contained, especially on the formulation side, you may have a turbulent-flow isolator. So I think it depends on the application and what you are trying to accomplish.

[Slide.]

Clean-air classifications; 10,000 for Class 100,000, background for an isolator. From an operational standpoint, when somebody says Class 10,000 area to me, I translate that into a Grade B area with air locking and gowning and everything else. When somebody says, "Do you think it is a good idea for me to put an isolator in a Grade B area?" I say, "Boy, that is the worst of both worlds," because an isolator is as fairly complicated piece of equipment.

If you want to do an isolator right, it has to be integrated functionally with the operation. You have air systems to integrate. You have decontamination systems to integrate and then you have to interact with it through gloves or through RTPs and all this other kind of stuff.

If you put that in a Grade B area so somebody is in full aseptic, you are making it much

harder to do that. Then it is like why do you have an isolator. So I kind of think that is a design nightmare and I know, if I were the operator in that area, I don't think I would like that very much whereas, if the operator is more comfortable and can interact with the equipment, I think you stand a chance of getting a better result.

I didn't address those comments just to air classification because, in some cases, if somebody has an older-style isolator, there may be a reason why they have that in what they may call a 10,000 air class. But I think a Grade C or a Grade D area, that Class 100,000 should be adequate for a production isolator especially if you consider that sterility-test isolators have been operating with excellent results in controlled nonclassified areas.

[Slide.]

Section C.1 talks about RTPs. I think, if the RTP is properly maintained, it should not cause an increase in contamination. However, you may want to limit interactions for process reasons. Like it is a lot easier if you can put a big container that will take a shift's-worth.

[Slide.]

I would like to get to one more, the decontamination. This is a six-log reduction. It is Section D.2. I think it depends on the isolator and the equipment inside. If you have stopper bowls and tracks that cannot be sterilized without opening the isolator, then I think it is a prudent thing to go for a six-log reduction. However, if you have an isolator that is used for handling presterilized components, I think a three-log reduction is adequate. So I think it depends on the application.

If my time is up, that's fine. There is only one more anyway.

DR. LEE: Thank you very much for studying the document so carefully.

MR. WIRCHANSKY: I do want to thank you for inviting me because I think it is important. Aseptic processing is very important and the idea of revising the guidelines is a chance for everybody to normalize expectations and raise the level in the industry. I just hope that, through these interactions, the agency will consider both the theoretical goal of raising the standards and also the practical applications of what people have to do when they work in these areas.

Thank you very much.

DR. LEE: Is there a question?

DR. BURSTYN: I have one question for you relative to the data you showed with the large number of manufacturers who are using a 10^6 kill, especially in light of the recommendation in PDA Technical Report 34 that talked about a three-log reduction. Can you speculate how much of that is really due to the lack of guidance and if it is somewhat a self-fulfilling prophecy where people are speculating on the 10^6 level based on, perhaps, Agency Issues 483s, or what may be a perception of what is expected by the Agency and other regulatory authorities?

MR. WIRCHANSKY: I think there is that concern that the client companies, or the people that I talk to, they want to get their processes approved. So, if they think that if they go a certain way, that their approval will be delayed six months or a year, they will probably weigh that against the extra work to do what they think is needed to satisfy the Agency.

On the other hand, it depends on what is going on inside the isolator. I used the example of the stopper bowls and tracks because that is a

part that directly contacts a product-contact surface. That is why I used the word "prudent." I think it is prudent to decontaminate those parts to a 10^{-6}.

But then I used, on the other side, if you have presterilized components, then essentially the bioburden should approach 0, when you put them in an isolator and then you do a decontamination, you probably just take an extra cycle or just--you are overkilling to what level when you have something that was essentially sterilized in the first place.

That is kind of where I was coming from on that.

DR. LEE: Thank you very much.

That concludes the Open Public Hearing. The next agenda item is on Manufacturing Issues Discussion.

Manufacturing Issues Discussion

DR. LEE: I think the format is there will be four presentations.

MR. FAMULARE: We have the question-and-answer session, actually, of the discussants on the agenda.

DR. HUSSAIN: The plan is to have FDA folks come and state the questions and focus the

discussion on the questions we have posed.

MR. FAMULARE: The first person who will be discussing the issues would be Kris Evans on sterilization options, an FDA investigator.

MR. FRIEDMAN: The agenda was actually supposed to include a discussion from the expert guests for twenty minutes followed by, then, Kris Evans' presentation..

DR. HUSSAIN: Vince, what that was, we were hoping the invited guests that we have, before Kris comes in, to sort of focus the questions, we would like to hear from them, the invited guests on their specific issues.

DR. LEE: Does everybody have the agenda? There is a big gap. That is why I was puzzled. So we have twenty-five minutes for discussion and we don't have to necessarily have formal presentations, just discussion.

DR. HUSSAIN: In a sense, I think what we would like to hear from the experts we have invited is their views on the concept paper and the questions that we have posed. Since we have twenty-five minutes, we have more time and we can use that time for them.

DR. LEE: So now it is clear. Mr. Munson.

Discussants

MR. MUNSON: I think many of the concepts and the issues that have been brought up before are still relevant. I do concur that, in some areas of the document, there needs to be more definition. I think media fills is a very, very large part of that. People are going to want to know specifics, how many to fill.

The issue of interventions is an extremely complex issue right now where I have to take 50,000 units worth of interventions and cram them into a 10,000 unit media fill which now really starts to make it look like I am validating something other than what I do normally.

I think this is something where there needs to be some balance. As you read the guideline right now, I have to take a full batch-worth of interventions, both number and type of intervention, and put those into my media fill. If we go with the concept that I am trying to validate what I would apply to a product, now I have deviated even from that and I have got something that has twice the interventions, or three or four times the interventions per number of units that I am producing.

It has also caused everybody to kind of go into some of the very weirdest media-fill processes where I have got some people that fill a few units and then do nothing and then fill a few more, and then do nothing. Then you have got the other kind that I fill some units, then I fill water units, then I go back to filling media, then back to water.

There are all sorts of permutations that are out there. I think it is really getting quite confusing so I think this is something where the guideline I think needs to be a little more specific and maybe reevaluate what it is we are trying to do.

We are trying to show the media fill and the process simulation is basically supposed to say that the process that I am going to supply to the product is capable of rendering a sterile product which is the product and the intent of doing this. So I think the process should be that I am going to do the normal number of interventions.

The number of units filled I think should be--you can come up with some function of what the batch size is because some processes, such as blow-fill seal, batch sizes can be 3 to 500,000

units is a batch. To do 5,000 units, this means I run the machine for five, ten minutes and I am done.

So I think some practical aspect could be devised that would allow me, for those kinds of processes, to have a larger media fill that would be more representative but yet not still be overburdensome to the industry.

So that is one aspect. I think the area of environment monitoring is another one that could use quite a bit of maybe further explanations, especially in the area of alert action levels and what do I do in response to those, could use with a little bit more because that is also a very confusing part in the industry.

So there are a couple of areas where I think more specifics would really assist the industry even without becoming too prescriptive but just giving guidance on what is the expectation, what is it that FDA wants to see when they come in to a facility.

I spend an inordinate amount of time dealing with those kinds of topics. They are very significant. One thing I was very happy to see, at least in this concept paper, is the emphasis on

doing trend analysis as part of that investigation and determining whether I need to do an extensive investigation of an environmental excursion or whether I don't have to do very much.

DR. LEE: Excuse me.

MR. MUNSON: Yes?

DR. LEE: Let me focus the discussion a little bit more. I think I might want to get my electronic gavel back, if necessary. But I don't think I need to. First of all, I think we only have about twenty-five minutes and there are six panelists here. We would like to hear from everybody.

MR. MUNSON: Okay.

DR. LEE: My fault. I did not make things clear. Moreover, we would like to hear your thoughts on design, control and contamination at this point.

MR. FAMULARE: That's right. The way we focussed the afternoon discussion is that, at least in this first part of the discussion, we will talk about design control and contamination, particularly the talk of Berit Reinmuller. And then we will go to sterilization options, personnel, environmental monitoring and media fills

and then have the panel be able to discuss each one of those.

So there was a break from Berit Reinmuller and there was a little confusion there. But we would like to at least focus this first part of the discussion until Kris Evans comes up on the design, control and contamination.

So we have all that media-fill comment and we will get back to answer that when we get to that discussion with Brenda Uratani leading that off. So if we could get the group to focus on those, starting with the design, control and contamination.

DR. LEE: Please.

MS. LOWERY: In terms of design, control and contamination, I think that the presentations given so far, in terms of the controls that have to exist in the aseptic-processing area in the critical zone are very important. Most of these focus, I guess, like we talked about a little earlier this morning on personnel being the major source of contamination in a clean room.

Once contamination is identified, obviously it is a little easier to deal with, but, in looking at the way people interact in an aseptic

process makes a big difference between a product's sterility and nonsterility.

So, in looking at the design aspects, I think that it is extremely important to look at the positioning of personnel in the critical zone, how they interact, to have their interactions be very well and clearly defined in standard operating procedures such that everyone knows how to intervene in the aseptic process with sterile tools and implements, et cetera, so that air flow is not disrupted and there is not the potential, then, to deposit particulate, viable and nonviable, into the aseptic product.

So that is a big concern is that the training of personnel, et cetera, in these areas as it relates to design control is something that may need to be a little bit more focused.

In terms of general contamination issues, in the clean room itself, I think there are several routes of contamination ingress into the aseptic-processing area. Certainly the biggest one is probably personnel. The other one is bringing materials and equipment into the area that go through an airlock or a pass-through and don't go through an autoclave or a dry-heat oven.

The potential for contamination there is great and usually I think what happens there in that particular scenario is that there is not a big focus on surface disinfection of these parts with a sporicidal as they ingress into the area. It results in the spread of contamination from one part to the surface of another through the operator. So the operator is basically a vector of contamination.

So I think that is a focus that needs to be brought up in terms of looking at the potential for controlling contamination in a clean room.

MR. FAMULARE: Do you have any specific suggestions in that regard toward the guidance as it is written, towards the concept paper?

MS. LOWERY: The concept paper could probably be a little bit more strengthened in terms of the particular aspect of the controls of bringing equipment and materials in through an airlock or through a pass-through. I think that has to be a qualified process. I think you have to use qualified disinfectants that have been shown to be effective against the bioburden that typically might be on these items as they are brought in. Then, the process, itself, should be qualified so

that there is complete assurance that there is no contamination being brought in that way.

There are other areas as it relates to personnel, then, in terms of gowning and what kinds of requirements maybe the guidance document should be strengthened on in terms of looking at gowning and the potential for people to bring in contamination which is the other viable route.

DR. LEE: Did you have something to add?

MR. MUNSON: Yes. On a design issue, I think a lot of us are focussing on the aseptic core. There is a huge part of most factories that is outside the aseptic core and, again, this is where the material movement and personnel movement--I think this is one of the weaknesses in the guide is this interaction between these areas that either support the aseptic core or are in front of it.

These are like putting transition points in between places like warehousing and then I start to move materials and personnel into a "manufacturing" area of the plant, maybe compounding areas, things of this--these are non-sterile areas, but I think it is critical to set up, from a design of a facility, transition

points where I have to do this decontamination or I have to try and retard contamination coming in from uncontrolled areas into cleaner areas.

So, the plant should be designed to get cleaner and cleaner as I get closer and closer to my aseptic-processing areas. I think this is something where the guideline really doesn't even get into that part of the facility and how that can play because that is all part of the "contamination control" aspects that should be built into a sterile manufacturing facility.

DR. LEE: Thank you.

Don?

DR. BURSTYN: I will try to be brief to leave some time for Mike at the end, here. I think that it is very--I want to make two points. First of all, we need to figure out a way to allow a more rapid implementation of new technology. It is clear that many of us go back to older technology because we are used to it and the agency is used to is and it is very safe for us.

We do avoid new technology because none of us really want to be a pioneer, the first one out there, and risk the chance of our approvals being delayed. Just a second fast point I want to make

is that reading through the document and hearing some of the talks, it is obvious that there are many parameters within a conventional fill room, within an isolator, of whatever, that we can monitor.

We can look at air flows at various areas. We can do environmental monitoring and such like that and we can collect a lot of data. We need to make sure that, just because we can collect data, that should not be the reason we are doing it. We need to make sure that the data we are collecting absolutely has some meaning to us and that we can use that data in order to help us to improve the quality of our processes and to ensure that better-quality products are getting to the end users, the patients.

So just because we can measure something, we shouldn't. We need to go back and really think about what we are doing.

I will leave it at that.

DR. LEE: Anne Marie?

MS. DIXON: I want to make a few comments on design. I think part of the problem starts when you don't lay out a process and then you don't have the adequate space in order to move items

throughout the facility. So the first thing that should be done is to analyze the process flow and then build the clean room or the controlled environments to suit the process.

When you try to shoe-horn it in, it gets to be very, very difficult. So that is going to give you a lot of entrances and egress areas for personnel movement and for things that go on to the areas. These are going to need multiple levels of control. Just adding a locker room two buildings over and having people tromp around through the outside in order to get over to the aseptic filling room doesn't work.

Yet, those are some of the things that people do every day. The same is true with bringing things off of trucks and then going through a passive airlock or passive pass-through and then assume it gets decontaminated.

So, having multiple stages of facilities, multiple egress and ingress points I think would be, in addition to the process flow would be very beneficial.

But then, when you get into the inside facility, I think we are having problems with things like smoke studies and trying to qualify

design. Smoke studies, certainly, in a passive situation, are much different than a dynamic condition which the two speakers earlier have shown us. But, not only that, the type of smoke could be a serious issue.

There are many smokes that are used today that are carcinogenic in nature and I think it is important for the Agency to understand that, that we just don't want smoke. We don't want a contamination thrown in the clean room just because we are trying to prove laminarity or unidirectional flow. But we want good science applied and want to actually see the movement of equipment, see the movement of people, and see the fact that the clean room can sweep items away.

That points back to having good filtration. Filtration is something that is very expensive today. Many firms, in their effort in order to cut back on costs, and "think green," are talking about reducing the velocities in the clean room, turning the clean room off at night and then going back to active condition in the next day.

This does seriously detrimental effects on a clean room. People are failing to go back to some of the original work that was done back in the

'70's and the '80's and the '90's by other industries in this clean-room field which have proven how you move particles, how you control particles, what happens to microbial during shut-down times, what happens when you reactivate fans.

So I think this whole science of the system and the design has got to be looked at very carefully. Otherwise, all the monitoring and all the training is going to be to no avail.

MR. FAMULARE: Again, do you have specific areas where you think the guidance needs to be beefed up in this area or changed?

MS. DIXON: I think it might be beneficial for the reader to have some references, in not just beefed up in some areas. I think we have got to address multiple use of airlocks. We have got to say something about using an active versus a passive unit. I think we have to say something about HEPA filters and making sure that these HEPA filters are tested with the appropriate standards by giving references.

We need to go back and reference some of the original work done by some of the aerospace people, some of the NASA people right here at

Goddard, which have proven what happens to clean rooms when they wind up being turned off at night and reactivated during the day. So the user can go back and look at this.

I think some enhancements on egress and ingress and some enhancements on references would be very helpful.

DR. LEE: Jeanne?

DR. MOLDENHAUER: I concur as far as this ingress/egress. I also support Sandy's comments about needing more guidance for validation of pass-through as this tunnel's disinfection and that as well. I am also concerned about just some of the things that are put in the guidance document; for example drains, and that drains are bad in clean rooms.

That is great, except that I have a lot of processes that are very moist in nature, compounding, washing componentry. If I don't have drains, then I have standing water in clean rooms which is not really a good thing. So I think we need to go back and look at that. I agree that it also needs more references.

DR. LEE: Mike?

DR. KORCZYNSKI: I sent my FDA colleagues

five pages of comments on the document so I am not going to reiterate those comments. I just wanted to play off some of the comments I heard today and maybe indicate some areas for inclusion in the concept paper.

One thing, for the sake of maybe providing some information to the panel, in some cases, I disagreed slightly with some of the speakers.

DR. LEE: Let us focus on design, control and contamination for now.

DR. KORCZYNSKI: Frankly, this is difficult to do, just given that direction in a moment. I would like to be able to just cite a few comments that I think are going to be beneficial to us. In this case, it was cited that aseptic individuals, perhaps, need better training and maybe the industry is derelict in that regard.

Well, I think people, in general, have to remember the industry has come a long way in aseptic processing. Along those lines, people receive yearly GMP training. People have to be validated in gowning. The industry, in many cases, has actual limits of 1 to 2 counts. It is getting to a point where basically the total process has basically improved.

If there is an area for potential improvement, if we look out in the next ten years, I would say that maybe would should consider a certified aseptic operator-training program, an aseptic certified program, for people who operate in manufacturing areas.

That could be developed by industrial associations in concert with the FDA and maybe an oversight could be the university that issues the certificate. But I think that that would give us some level of standardization among all operators regardless of whether they are with a small firm or large firm.

The other issue I found relative to the document, a key one. It is just like many of my colleagues said. I found it wanting in terms of not saying anything about the action levels relative to media fills. To those that are unacquainted, a media fill is a way of replicating the process and giving you some feeling that you have validated the process.

It is not the total answer but it is a pretty good answer. Of course, there has been an arbitration through this through the years. Many people classically have been using a 10 percent

mathematical approach. I think where the industry has improved is that, in my own experience, there seems to be a target level of 0 out of 3,000.

As a matter of fact, people have moved that up to wanting to see no positives out of units 3,000 to 6,000. Companies feel uncomfortable when then get one to three positives out of about 6 to 9,000 units. I think everyone feels uncomfortable in an initial validation if you have a hiccup in three replicate runs, whether that be one positive or three. That is inadequate. You have to go back until chronologically or sequentially you have three good runs.

So I think the document needs to address something along those lines. The other place where I found it wanting is what about the clinical fills. What about operations that are filling small clinical units, 500 to 1,000 units, basically? When do you conduct a media fill there? I would say that the isodocument on aseptic filling has a section that should be considered and reviewed.

Relative to this discussion on limits and levels, I think that that can be variable. I am frankly a proponent of limits because, in many

cases, many companies put their environmental counts in their specifications because it becomes part of their work-order procedures as well.

Basically, I think that one item I asked for inclusion in the document and it will appear stringent on the part of some of my industrial colleagues, but I think there should be a management review. When you have a number of counts that exceed your limits or levels in the Class 100 area, there should be some arbitration as to whether you are going to release that product or not, because now we are holding these environmental counts to be absolute rather than a trending analysis type of an approach.

So that was a suggestion.

I am going to answer one gentleman's question about sterility testing, the amount of positive units and all that we saw on the chart. I would say that, in my opinion, I don't think those were all reflective of sterility-testing failures because we know the industry has improved in sterility testing because many companies are now using isolators rather than the testing room to test the product.

As a matter of fact, one failure in the

initial test means that product is gone.

Just the other comment relative to barrier isolators, maybe what we could include in the document. There was discussion of these classical technologies versus barrier isolators. However, there is a hybrid and that hybrid is the conventional filling line where one may put a plexiglass cabinet around it. One may put curtains around that, so it is not truly and enclosed isolator but it prevents manual intervention during the filling of the product and, surprisingly--not surprisingly; in many cases, those data are excellent in that environment.

So that, in summary, is it.

DR. LEE: Okay; very well. What I have heard is the writers of this draft concept paper would like to have some specifics which I don't think is forthcoming, per se. But you hear the sentiment.

MR. ELTERMAN: One of the things I wanted to add to the design and controls is one of the things we did wrestle with, what was going to be included as part of the scope of the document. To answer some of the questions related to the HVAC, we sort of have that on a parallel track as a

separate guidance document that we see coming out about the same time.

We weren't in a position to present it here but, again, some of the various aspects of that will be covered in a separate guidance document.

DR. LEE: The philosophy of this is to be as broad as possible, to cover as many bases as possible.

MR. ELTERMAN: When taking a look at scope of this, we realize that there are additional things that we needed to have built in which would be probably best for a separate guidance document. So there was a lot of crossover between what could have been included in the aseptic process guidance document and the HVAC document.

So we haven't finalized that yet to bring it forward, but there has been a lot of cross-talk to try to make sure that the two documents harmonize which may address some of the issues that we have heard today, at least with respect to the HVAC controls.

MR. MUNSON: I guess, just from a design aspect, though, one of the things would have been this harmonization on the ISO designations. I

guess the biggest push for that is the harmonization effort. One of the things that is not in the document is doing a conversion from European 209 and ISO because that has got to be one of the most confusing things the identify has been wresting with is doing that conversion, because the European designations have an inoperation and a static mode and it's okay, and which one are we referring to.

People mix those up. They are using Class B's as being equivalent to a Class 100 U.S. But, again, we are mixing those up. So I think the document, if you were going to go back and relook at it, would be to do the isodesignations throughout the document and then just have a really small table in the front that would do the conversions as to what that means in the old terms and in the current European system, so that everybody would be very, very clear on what you are talking about.

But moving the rest of the document into the ISO which is slated to be the harmonized classification system.

DR. LEE: Comments?

MR. ELTERMAN: Again, that was one of the

discussion points that we had as part of the committee, how far did we want to go in looking at ISO. Certainly, there are concepts that are compatible with our document. We just weren't, at this point, ready to look at ISO and sort of embrace that. So that is a separate discussion probably yet to come but I certainly appreciate your comments on that fact.

MR. MUNSON: I am only talking about the classification scheme. I am not saying that you have to endorse the entire document. FDA never endorsed 209 in its entirety, but just the classification as to what do I call what, I think, is the aspect that I am looking for right now. Whether you endorse the entire Part 1, Part 2; yes, you can do that at some other point

MR. ELTERMAN: We tried to make reference to it as part of the table but, in as much as that has caused some confusion, we will go back and look at that.

MS. DIXON: In that you are going to be writing a parallel design document, then I have two design questions for you. There are two comments that are in--one is in Section C. It is actually listed as Line 170 which, actually, exceeds some of

the current standards. I think the industry would like a clarification of what you mean by 0.05 inches water gauge from room to room, because currently most people are following what was written in 1987 and in between the critical and the noncritical, that's true and in between the noncritical and the ambient, that is true but most people practice cascade between that.

If we are looking at going to 0.05 inches water gauge from room to room, then some facilities are not going to be able to meet that criteria even though they been licensed using the cascade. So I think that is an area that will need the committee to go back and look at it for clarification.

The second point for clarification under design, if I could refer the committee over to the next page, Page 6, under Line 240, this is also a deviation from what the industry has seen in the replacement of a HEPA filter should there be a significant leak.

In general, FDA has embraced the IST document, recommended Practice 6.2 in its use of a percentage and a size limitation. PDA has since even quoted some of that in some of their documents. So my question, again, to the committee

is are we moving towards a change? Are we raising the bar? Was that your intent or is it just a matter of semantics.

MR. FAMULARE: We did discuss these areas quite a bit internally. I could look to one of the technical people that worked on it to maybe come to the microphone if they want to clarify these points.

DR. LEE: Are you looking for volunteers?

MR. FAMULARE: I think either Rick or Kris.

DR. LEE: While Kris is coming to the microphone, let me give you a preview about what is ahead. We have four other topics, sterilization options, personnel and environment monitoring and media fills to discuss. Is that right?

MR. FRIEDMAN: I am just reading on the spot, just to refresh my memory on exactly how it was stated. We used the concept that areas of different criticalities should generally--that is one of the places where we used the qualifying word--generally have a 0.05 positive differential pressure relative to areas of lower criticality. But the word generally was used there to allow for latitude for firms who want to use something like

0.03 or something like that so they don't have to keep stepping up each from one room to one room to one room.

We do want to see the progressive pressure cascade from the area of lowest criticality to the area of the highest criticality as a well-accepted facility-control concept. If there is a need for clarification in the guidance, we could go back and, as we prepare to issue draft guidance, we can, perhaps put the example of the aseptic-processing clean room and its adjacent lesser-classified room in there as the most prominent example, the way it was in the original '87 guidance.

There are other options available, also, that we could consider. But we think they were generally provided for those instances and that is why we put the word there.

DR. BURSTYN: I think, in a way, it kind of points out that we have to be exceedingly careful and very deliberate when we choose our precise wording in this because this is often open to interpretation. Not only is this, in effect, going to served as a guidance for industry, often these documents actually become manuals for inspectors when they are coming into your plant.

MR. FRIEDMAN: When you have the word "generally," the advantage of the firm is that they can throw back those words and quote them to FDA in a 483 response. That is one of the reasons it is a side effect or byproduct of this guidance document, but it is an advantage for firms that they can then quote this document and say, "Well, FDA says 'generally' in their guidance document."

Also, we have seen a number of firms that, in areas besides--and this is one of the reasons why we have changed the guidance relative to only giving on example in the original '87 guidance, or we plan to change it, because we have seen a number of firms that have had a progressive cascade between an area such as the unclassified corridor that leads often through an airlock into the aseptic-processing facility, the introduction to the aseptic-processing facility.

This is another area where 0.5 inches of water gauge is typically used. So this is what we were trying to reflect in this guidance. It was supposed to be, instead of giving one narrow example, as in the '87 guidance, we were giving more of a reflection of the current status of the pressure cascade used by the industry for

contamination control.

So, again, there are a number of ways to approach this but I also do take your comment on improving the precision of the words.

DR. BURSTYN: I appreciate your response but also please remember we would actually prefer not to get a 483 than to have a great response to it.

MR. FRIEDMAN: Good point.

DR. LEE: Very well. What I propose to do--we are going to take a break. We are going to take a fifteen-minute break ahead of schedule, and then we will come back here at 2:40 and continue from there.

[Break.]

DR. LEE: Let me remind everybody about what was the general intent of the agenda. There is a concept paper for all of us. I think the authors of the paper would like to hear from us whether or not the document, as written, is scientifically sound.

I have no idea what the intent of this document is going to be. I think it is a guidance of some sort. Also, we just heard earlier there would be parallel documents developing.

Before the break, I was just curious to know what roll would the committee, on the same side of this table, play. I don't want them to say that we are not involved and take off. Obviously, we would like them to participate, like the committee to participate. I would like you to listen carefully from the experts, and then advise our colleagues as to which way to go, tell them your preference of a specific document or something flexible, and whatever you think would be scientifically sound.

That is want I planned to say. Now, the next person on the agenda is Kris.

Sterilization Options

MR. EVANS: Good afternoon.

[Slide.]

I am Kris Evans. I am a field investigator with ORA located in Philadelphia. I was also on the committee to redraft this document. It is my pleasure this afternoon to talk to you a little bit about sterilization options available to the manufacturers of sterile products.

[Slide.]

The Agency recognizes there are options available. Really, there are two principles to,

terminal sterilization and aseptic processing. However, it is very important to emphasize that, in offering this document as a guidance to industry, we did not to intend to imply that aseptic processing could be used as a suitable alternative to terminal sterilization where feasible.

Indeed, and really especially in light of the Agency's initiative to science-based risk management, aseptic processing continues to be a sterilization option of last resort.

[Slide.]

In the concept paper, in the scope section, we have included two statements in this regard, the first one basically points out, "It is a well-accepted principle that sterile drugs should be manufactured by aseptic processing only when terminal sterilization is not feasible," and, further on in that paragraph, "If it is not possible to terminally sterilize adjunct processing steps to increase the levels of sterilization confidence should be considered."

[Slide.]

I just want to briefly review some of the science behind our position but, before I do that, there are a number of terms in the sterilization

science arena, and I just want to mention two to help facilitate this discussion.

The first one is PNSU. It is the probability an individual unit will be non-sterile after the application of a lethal agent. So when we say a PNSU of 1 in 10^6, that means the probability that a unit is nonsterile is 1 in a million.

The second term is F_o or the sterilization process equivalent time. It is the equivalent number of minutes as 121 degrees Celsius delivered to a unit by a sterilization process. So the term, an F_o equal to eight minutes is saying that a cycle delivered the equivalent microbial lethality of 8 minutes at 121 degrees.

Since cycles are not always run at 121 degrees and there is lethality accumulated during heating up and cooling down, this F_o term enables us to compare different cycles under standardized terms and the probability of the non-sterile unit concept allows us, since demonstration of sterilization is not an absolute but is talked of in terms of probability, we use this term.

Historically, a probability of a nonsterile unit of 1 in a million, or greater, has

been the threshold for sterility by terminal sterilization.

[Slide.]

To address the question of is this, indeed, happening in industry, do we have instances where firms are aseptically processing product where terminal sterilization is feasible, the Agency doesn't really have information on that. But a recent PDA Technical Report No. 36, which surveyed the industry, asked this specific question at your site; "Is aseptic processing used for products that could be terminally sterilized?" They defined the "could be terminally sterilized" as "capable of receiving an F_o greater than or equal to eight minutes in its current configuration."

[Slide.]

The response to that question showed that approximately one-third of the firms, indeed, have products that meet that criteria and, of those firms, the side bar to the side shows that 2 to 85 percent of their products are affected. So if, indeed, your firms are processing aseptically where terminal sterilization is feasible, that is happening with 2 to 85 percent of their products.